Complete Summary

GUIDELINE TITLE

The role of octreotide in the management of patients with cancer.

BIBLIOGRAPHIC SOURCE(S)

Systemic Treatment Disease Site Group. Major P, Figueredo A, Tandan V, Bramwell V, Charette M, Oliver T. The role of octreotide in the management of patients with cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Aug [online update]. 30 p. (Practice guideline report; no. 12-7). [57 references]

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Chemotherapy-induced diarrhea
- Post-operative complications following surgery for pancreatic cancer
- Carcinoid and other neuroendocrine tumours
- Chronic bowel obstruction due to advanced cancer

- Advanced malignancies (metastatic breast cancer; advanced colorectal, stomach, or pancreatic cancer; or unresectable malignant hepatoma)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management

CLINICAL SPECIALTY

Gastroenterology
Oncology
Pharmacology

INTENDED USERS

Pharmacists
Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate if treatment with octreotide has advantages over standard measures in controlling diarrhea induced in cancer patients by particular chemotherapy regimens
- To evaluate if therapy with octreotide can reduce complications and mortality after surgery for pancreatic cancer
- To evaluate if patients with carcinoid and other neuroendocrine tumours secreting vaso-active substances can be treated with octreotide to relieve debilitating symptoms and improve quality of life and/or survival
- To evaluate if treatment with octreotide can help relieve chronic bowel obstruction, avoid the use of nasogastric tubes, and improve quality of life in terminally ill cancer patients
- To evaluate if treatment with octreotide as an anti-tumour agent improves outcomes such as tumour response, quality of life, and survival in patients with advanced malignancies

TARGET POPULATION

- Adult cancer patients receiving chemotherapy, including 5-fluorouracil (5-FU) and/or cisplatin, who have developed diarrhea sufficiently profuse to put them at risk for dehydration (generally National Cancer Institute Common Toxicity Criteria grade 3/4)
- Patients undergoing pancreatic surgery for pancreatic cancer
- Patients with carcinoid and other neuroendocrine tumours who have had no improvement in symptoms following chemotherapy or those who present with debilitating neuroendocrine symptoms (i.e., profuse diarrhea)
- Terminally ill cancer patients with inoperable bowel obstruction
- Patients with metastatic breast cancer, advanced colorectal, stomach, or pancreatic cancer, or unresectable malignant hepatoma

INTERVENTIONS AND PRACTICES CONSIDERED

1. Octreotide therapy
2. Standard therapy such as loperamide (for diarrhea), scopolamine butylbromide or hyoscine butylbromide (for bowel obstruction), or best supportive care

MAJOR OUTCOMES CONSIDERED

- Complications and mortality after surgery for pancreatic cancer
- Tumour response
- Quality of life
- Survival
- Symptom relief or control
- Adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature was searched using the MEDLINE (Ovid) (1966 through November 2002), CANCERLIT (Ovid) (1983 through November 2002), and Cochrane Library (Issue 4, 2002) databases. In addition, the Physician Data Query clinical trials database, and abstracts published in the conference proceedings from the meetings of the American Society of Clinical Oncology (1995–2002) and the European Society for Medical Oncology (1998, 2000) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for relevant clinical practice guidelines. Reference lists from relevant articles and reviews were searched for additional trials. The literature search combined disease specific terms (neoplasms/ or cancer:.mp. or carcinoma:mp. or malignan:.mp. or tumo?r:.mp.) with treatment specific terms (octreotide/ or octreotide.mp. or somatostatin.mp. or sandostatin.mp. or SMS-201-995.mp.) and search specific terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and clinical trials.

August 2004 Update

The original literature search has been updated using MEDLINE (October 2002 through July 2004), EMBASE (September 2002 through July 2004), the Cochrane Library (Issue 2, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (2004), and the European Society for Medical Oncology (2002). Article bibliographies and personal files were also searched to July 2004 for evidence relevant to this practice guideline report. Please note that CANCERLIT is no longer included in update searches: results from an internal Practice Guidelines

Initiative project indicated that the overlap with MEDLINE is 100%, making CANCERLIT database searches redundant.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Randomized trials comparing octreotide with placebo, observation, or other treatment in cancer patients for the indications mentioned in the guideline questions
- Non-controlled reports of octreotide were considered only for questions three (neuroendocrine tumours) and four (chronic bowel obstruction).
- Outcomes of interest, including tumour response, survival, symptom relief or control, and quality of life were reported.

Exclusion Criteria

- Letters and editorials were not considered.
- Papers published in a language other than English were not considered.

NUMBER OF SOURCE DOCUMENTS

Treatment of Chemotherapy-induced Diarrhea

Six randomized trials and two practice guidelines were reviewed.

August 2004 Update

One additional randomized trial (reported as an abstract) was reviewed.

Octreotide Following Pancreatic Surgery

Three large, multicentre, placebo-controlled, double-blind randomized trials were reviewed.

August 2004 Update

Three additional trials were reviewed.

Symptom Relief of Carcinoid and Other Neuroendocrine Tumours

Five randomized trials, one clinical practice guideline, and one systematic review of dose-titration data were located and were eligible for review.

Octreotide in Patients with Chronic Bowel Obstruction

Two small, randomized trials and three single-arm studies were reviewed.

August 2004 Update

One additional randomized trial was reviewed

Octreotide as an Anti-tumour Agent in Advanced Malignancies

Nine randomized trials were reviewed.

August 2004 Update

One additional randomized trial was reviewed

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The results of three randomized trials comparing octreotide to loperamide for the resolution of chemotherapy-induced diarrhea were pooled, using the meta-analytic software program RevMan 4.1 (Metaview© Update Software). Pooled results were expressed as a relative risk (RR) with a 95% confidence interval (CI) and percent relative risk reduction (RRR). Relative risk reduction compares the risk of target events in the treatment group with the risk of target events in the control group (RRR=1-RRx100); Relative risk ratio measures the proportion of patients in the experimental group, relative to the proportion of patients in the control group, who are likely to experience the event. When the event measured is unfavourable (e.g., diarrhea), estimates greater than 1.0 favour the control group (e.g., loperamide therapy), and estimates less than 1.0 favour the experimental group (e.g., octreotide therapy). The fixed effects model was used in the meta-analyses because there were too few studies to estimate random effects. A statistical Q-test was used to measure statistical heterogeneity.

It was judged inappropriate to pool the results of any other section because of extensive heterogeneity in trial design and reporting of outcomes of interest.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

When octreotide was first considered as a guideline topic for the Systemic Treatment Disease Site Group (DSG), five different indications for the drug in patients with cancer were discussed. Data were available on the use of octreotide as an anti-tumour agent, in chemotherapy-induced diarrhea, in pancreatic surgery, in neuroendocrine tumours, and for chronic bowel obstruction. The group decided to combine all the indications for octreotide into one single report, rather than producing a separate report for each of the various indications.

A preliminary literature search was conducted to locate randomized trials for each of the above-mentioned indications. The amount and quality of the data located varied for each indication. For the neuroendocrine tumour section, the only randomized data involved patients with carcinoid tumours. The group wanted to know if there was any evidence that octreotide was active in other neuroendocrine tumours, and so another literature search was performed to locate non-randomized trials of octreotide use in non-carcinoid neuroendocrine tumours. At the time that the first literature search was conducted, there were no randomized trials available on the use of octreotide in chronic bowel obstruction. The group decided to conduct a search for reports of non-randomized trials for this indication and to provide a summary of the evidence but to make no actual recommendations for this section. Since that time, two small, randomized trials have been published on the use of octreotide in chronic bowel obstruction, and the group decided to make a recommendation for this section. Members of the Systemic Treatment Disease Site Group agreed with the recommendations that were developed for the other sections of the guideline.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 152 practitioners in Ontario (141 medical oncologists and eleven surgeons). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Systemic Treatment Disease Site Group.

The practice guideline report was circulated to 13 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Ten members of the PGCC returned ballots. Seven members approved the practice guideline report as written. Two members provided suggestions for consideration, and one member approved the report conditional upon a re-wording of one of the recommendations.

The practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Octreotide in the Treatment of Chemotherapy-Induced Diarrhea

- For chemotherapy-induced diarrhea, octreotide is recommended at a dose of 100 micrograms subcutaneously three times daily and escalating every eight hours by 50 to 100 micrograms until the diarrhea is controlled, to a maximum of 500 micrograms three times daily.

Octreotide Following Pancreatic Surgery

- Octreotide, administered at a dose of 100 micrograms subcutaneously three times daily starting one hour prior to surgery and continuing for seven days is recommended as part of the standard management for patients undergoing pancreatic surgery.

Octreotide for Symptom Relief of Carcinoid and Other Neuroendocrine Tumours

- Octreotide is recommended to control symptoms associated with carcinoid tumours.
- Because the mechanism of action and the pathophysiology of other secretory neuroendocrine tumours are similar to that of carcinoid tumours, it is reasonable to recommend octreotide to control symptoms associated with secretory neuroendocrine tumours.
- It is suggested that octreotide be administered in a subcutaneous dose of 100 micrograms three times daily, or 200 micrograms twice daily, with an increase in the dose of 50 to 100 micrograms every eight or twelve hours until symptom control is achieved.

Octreotide in Patients with Chronic Bowel Obstruction

- In patients with inoperable bowel obstruction due to advanced cancer, the use of octreotide 300 micrograms daily by subcutaneous infusion may be considered for the purpose of reducing symptoms such as nausea, vomiting, and pain, as well as the need for a nasogastric tube.

Octreotide as an Anti-tumor Agent in Advanced Malignancies

- Octreotide cannot be recommended as an anti-tumour agent for the treatment of metastatic breast cancer, advanced pancreatic, or asymptomatic colon cancer.
- Further studies in advanced breast, colon, or pancreatic cancer are unlikely to be productive unless a different formulation or dose schedule is anticipated to be more active.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Octreotide in the Treatment of Chemotherapy-Induced Diarrhea

- In four small randomized trials, octreotide controlled diarrhea induced by chemotherapy with 5-fluorouracil (5-FU) and/or cisplatin significantly better than loperamide.
- When data on complete resolution of chemotherapy-induced diarrhea from three randomized trials were pooled, there was an observed benefit for octreotide when compared with loperamide (overall risk ratio, 0.16; 95% confidence interval, 0.08 to 0.34; $p<0.0001$).

Octreotide Following Pancreatic Surgery

- In three large, placebo-controlled double-blind randomized trials, there were significant decreases in serious complications (pancreatic fistula, abscess, and fluid collection) in the patients receiving octreotide. There were no differences between octreotide and placebo in mortality following surgery in any of the trials.

August 2004 Update

- Three randomized trials identified in an update of the literature did not detect any significant differences in serious complications or mortality with the addition of octreotide to surgical resection.

Octreotide for Symptom Relief of Carcinoid and Other Neuroendocrine Tumours

- In three small randomized trials, octreotide significantly reduced episodes of flushing and diarrhea in patients with secretory carcinoid tumours. Short-acting octreotide was compared with placebo in three trials, different doses of a long-acting formulation in the fourth, and to lanreotide (a long acting somatostatin inhibitor) in the fifth.
- Small studies in other neuroendocrine tumours suggest that symptoms associated with hormonal secretion can be improved with octreotide administration.

Octreotide in Patients with Chronic Bowel Obstruction

- Two small randomized trials, one comparing octreotide to hyoscine butylbromide and the other to scopolamine butylbromide, were reviewed. Three single-arm studies were also reviewed. The data from the randomized trials demonstrated superior symptomatic relief for octreotide compared with butylbromide in terms of nausea, vomiting, pain, and nasogastric secretions.

August 2004 Update

- One trial detected significant differences in favour of octreotide over hyoscine butylbromide for episodes of vomiting and nausea from time 1 to time 2, and in fatigue and anorexia in relation to symptom improvement. No significant differences in pain were reported between the two treatment groups.

Octreotide as an Anti-tumour Agent in Advanced Malignancies

- Early encouraging results of small randomized trials in patients with metastatic breast and gastrointestinal cancer have not been confirmed by larger, tumour-specific trials in breast, colon, and pancreatic cancer.
- A small randomized trial in patients with malignant hepatoma demonstrated improved survival and symptom control in patients receiving octreotide. These results should be regarded as preliminary and further randomized trials are needed.

August 2004 Update

- For patients with advanced hepatocellular carcinoma, one small randomized trial did not detect any significant survival benefit with octreotide when compared with control.

POTENTIAL HARMS

Octreotide in the Treatment of Chemotherapy-Induced Diarrhea

- Adverse effects attributed to octreotide treatment were reported in two trials. Gebbia et al reported that 15% of patients receiving octreotide had pain at the injection site, and 15% of patients receiving octreotide experienced mild abdominal pain. Gellar et al reported two patients with mild elevations in total bilirubin, which resolved following completion of octreotide treatment. Another patient in this trial experienced abdominal cramping.

Octreotide Following Pancreatic Surgery

- Montorsi et al reported two patients with nausea, two patients with vomiting, one patient with diarrhea, and one patient with prolonged postoperative bowel transit. Three of these patients received octreotide and three received placebo. Treatment was not discontinued in any of these patients.
- Bassi et al reported four patients with adverse effects related to octreotide treatment. One patient developed a skin rash and fever, and treatment was subsequently withdrawn. One patient developed a skin rash without fever, vomiting occurred in another patient, and biliary sludge in a third.

August 2004 Update

- In the three additional randomized trials identified, no adverse events directly related to treatment with octreotide were reported.

Octreotide in Symptom Relief of Carcinoid and other Neuroendocrine Tumors

- Jacobsen and Hanssen reported on one patient who developed severe facial, leg, and arm edema with dyspnea when treated with octreotide. Treatment was discontinued. Another patient experienced severe nausea during the first four weeks of treatment; this patient left the study. Moderate degrees of headache, chest pain, abdominal discomfort and anxiety were reported, but more adverse effects were reported during the placebo period than the octreotide period.
- In a trial reported by Oberg et al., adverse effects following octreotide administration included borborygmia and flatulence.
- In a trial reported by Rubin and colleagues, the only adverse effects that were considered related to octreotide treatment were abdominal pain in one patient, flatulence in two patients, nausea in three patients, and steatorrhea in one patient.
- Mild episodes of abdominal pain and/or nausea and emesis were reported in 29% of patients receiving octreotide and in 14% receiving lanreotide in a trial reported by O'Toole et al.
- Commonly reported adverse effects attributed to octreotide in 15 non-controlled trials included pain, diarrhea, vomiting, steatorrhea, hyperglycemia, gallstones, and local skin irritation.

Octreotide in Patients with Chronic Bowel Obstruction

- Mangili et al reported no important side effects related to octreotide treatment. Mercadante et al reported pain at the injection site in 50% of the patients and an uncomplicated skin reaction in one patient. Khoo et al reported no adverse effects due to treatment with octreotide.

Octreotide as an Anti-tumour Agent in Advanced Malignancies

- Side effects of octreotide treatment were recorded in most of the trials (Table 2 in the original guideline document). Common complaints included nausea, diarrhea, vomiting, steatorrhea, and abdominal cramps.

- In the trial by Bontenbal et al, 40 to 50% of potentially eligible patients with advanced breast cancer refused randomization because of the three daily injections. In the trial by Ingle et al, 22% of patients with advanced breast cancer receiving tamoxifen and octreotide reduced, stopped, or did not comply with the octreotide treatment regimen. Seven patients discontinued treatment because of gastrointestinal complaints (four cases), weight loss and anorexia (one case), severe hot flushes (one case), and refusal (one case). Three patients reduced their octreotide dose because of diarrhea (two cases) and musculoskeletal pain (one case). In the trial by Goldberg et al, the dose of octreotide was reduced in 5% of patients because of diarrhea and steatorrhea. Kouroumalis et al reported that four patients discontinued treatment because of the required twice-daily injections of octreotide.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

Octreotide in the Treatment of Chemotherapy-Induced Diarrhea

For patient convenience, an alternative, albeit less effective, option is standard oral anti-diarrheal agents in the usual approved doses (e.g., loperamide 4 mg initially, then 2 mg after every unformed stool, up to a maximum of 16 mg/day). If the diarrhea has not substantially improved in 24 hours, or if the patient requires intravenous rehydration, then octreotide should be initiated.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Systemic Treatment Disease Site Group. Major P, Figueredo A, Tandan V, Bramwell V, Charette M, Oliver T. The role of octreotide in the management of patients with cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Aug [online update]. 30 p. (Practice guideline report; no. 12-7). [57 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 May 7 (revised 2004 Aug)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Systemic Treatment Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Systemic Treatment Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of octreotide in the management of patients with cancer. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on January 23, 2004. The information was verified by the guideline developer as of February 23, 2004. This NGC summary was updated by ECRI on March 3, 2005. The information was verified by the guideline developer on March 16, 2005.

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